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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/KR99/00381</p> <p>(22) International Filing Date: 19 July 1999 (19.07.99)</p> <p>(30) Priority Data:  1998/0029151 20 July 1998 (20.07.98) KR  1999/0028866 16 July 1999 (16.07.99) KR</p> <p>(71)(72) Applicant and Inventor: MOOK, Inhee [KR/KR];  301-101, Kumho-Apartment, Yangji-maeul, Sunae-dong,  Bundang-ku, Sungnam-si, Kyungki-do 463-020 (KR).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): HUH, Kyoan [KR/KR];  69-34, Yeonhee 3-dong, Seodaemun-ku, Seoul 120-113  (KR). JOO, In-soo [KR/KR]; 103-2001, Ssangy-  ong-Apartment, Galak 2-dong, Songpa-ku, Seoul  138-747 (KR). JUNG, Min-whan [KR/KR]; 301-101,  Yangji-maeul, Sunae-dong, Bundang-ku, Sungnam-si,  Kyungki-do 463-020 (KR).</p> <p>(74) Agent: KIM, Young-chol; Korea Coal Center, 10th floor, 80-6,  Susong-dong, Chongro-ku, Seoul 110-727 (KR).</p>	<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG,  BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB,  GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,  KP, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,  MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,  SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA,  ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ,  UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD,  RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK,  ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI  patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR,  NE, SN, TD, TG).</p> <p><b>Published</b>  <i>With international search report.  Before the expiration of the time limit for amending the  claims and to be republished in the event of the receipt of  amendments.</i></p>	
<p>(54) Title: THERAPEUTIC AGENT FOR DEMENTIA, COMPRISING GINSENG EXTRACT</p>		
<p>(57) Abstract</p> <p>Disclosed is a therapeutic agent for dementia and a method for treatment of dementia. It comprises as medicinally effective component the ginsenoside Rb1 or Rg1, both being ginseng extracts. The therapeutic agent has an efficacy against neuronal cell death ascribed to beta-amyloid, a fundamental factor causing dementia such as Alzheimer's disease, by virtue of the advantages of the ginsenoside Rb1 and Rg1 acting specially on the hippocampus to activate the formation of synapses as well as the signal transduction between synapses, leading to an improvement in learning and memory.</p>		

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WO 00/04912

PCT/KR99/00381

**THERAPEUTIC AGENT FOR DEMENTIA, COMPRISING GINSENG  
EXTRACT**

5

**Field of the Invention**

The present invention relates to a therapeutic agent for dementia, comprising a ginseng extract as a medicinally effective component and a method for the treatment of dementia which comprises administering a ginseng extract.

10

**Description of the Prior Art**

The fundamental cause of dementia resides in neuronal cell death. In view of this point, conventional medicines which have been used to treat dementia cannot be said to be genuine therapeutic agents because they all function only to enhance the activity of acetylcholine, a neurotransmitter, but are unable to prevent neuronal cell death itself. It is true that, in an early stage of dementia, the neuronal cells

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WO 00/04912

PCT/KR99/00381

in which acetylcholine is implicated as a transmitter are damaged. However, dementia is also caused by the damage of the neuronal cells in the electric transmission mechanism of which other neurotransmitters, such as glutamate, are  
5 involved. Therefore, increasing the activity of acetylcholine shows a temporary effect only for the patients who are in the early stage of dementia.

Since glutamate serves as a neurotransmitter with the most abundance in the brain, it is expected that a glutamate  
10 activator, if it is developed, could have more potent activity against dementia than could acetylcholine activators. However, the glutamate activator functions only to enhance the interaction between the neurons which still remain intact after the occurrence of neuronal cell death,  
15 rather than prevent the neuronal cells from being damaged. Accordingly, the glutamate activator cannot be a fundamental therapeutic agent.

Extensive clinical and genetic research have recently been directed to dementia, indicating that, when beta-

WO 00/04912

PCT/KR99/00381

amyloid is accumulated in the brain, it damages neuronal cells, leading to causing dementia such as Alzheimer's disease.

In order to cure dementia, therefore, there is a strong  
5 demand for the development of a therapeutic agent which can restrain beta-amyloid from being formed as well as eliminate the toxicity of beta-amyloid.

#### Disclosure of the Invention

10 It is, therefore, an object of the present invention to overcome the above problems encountered in prior arts and to provide a dementia-curing agent which is able to prevent the neuronal cell death attributable to the accumulation of beta-amyloid in the brain and regenerate the neuronal cells  
15 which are undergoing a cell death program.

In accordance with the present invention, the above object could be accomplished by a provision of a therapeutic agent for dementia, comprising ginsenoside Rb1 or Rg1 as a medicinally effective component.

WO 00/04912

PCT/KR99/00381

The intensive and thorough research on the prophylaxis and treatment of dementia, repeated by the present inventors, resulted in the finding that ginseng extracts, especially ginsenosides Rb1 and Rg1, are strongly preventive  
5 of neuronal cell death attributable to beta-amyloid and curative of neuronal cell damage.

From ancient time, ginseng has been used as a crude drug in the Orient. Now, ginseng is found to produce no harmful effects. With this advantage in mind, the present  
10 invention utilizes ginseng extracts, especially ginsenosides Rb1 and Rg1, in treating the neuronal cell damage ascribed to the accumulation of beta-amyloid.

**Brief Description of the attached Drawings**

15 The above and other objects, features and other advantages of the present invention will be more clearly understood from the following detailed description taken in conjunction with the accompanying drawings, in which:

WO 00/04912

PCT/KR99/00381

Fig. 1 is a graph showing the results of the space perception ability test using the Morris water maze technique for the control and the test groups administered with ginsenosides Rg1 and Rb1;

5 Fig. 2 shows Western blots of synaptophysin 38 kDa in molecular weight, obtained from the control and the groups administered with ginsenosides Rb1 and Rg1; and

Fig. 3 is a histogram showing the average synaptophysin levels, along with the standard deviations, in the  
10 hippocampus and the cortex for the control, the Rb1-administered group and the Rg1-administered group.

#### Modes for Carrying Out the Invention

Below, a detailed description will be given of the  
15 curative effect of ginsenosides Rb1 and Rg1 on dementia, which was demonstrated by the experiments the present inventors had performed.

A better understanding of the present invention may be obtained in light of the following examples which are set

WO 00/04912

PCT/KR99/00381

forth to illustrate, but are not to be construed to limit the present invention. In the following examples, an *in vitro* experiment was described in Example I while the ginsenosides were directly administered to test animals in  
5 Example II (*in vivo* experiment).

#### EXAMPLE I

There was established a system in which neuronal cells were growing, but showed a cell death program when being  
10 added with beta-amyloid. An examination was made of whether the cell death program of the neuronal cells was prevented or ceased or not when they were subjected to the pretreatment, cotreatment or posttreatment with a crude ginseng extract, commercially available from Sigma Co.,  
15 U.S.A., with the standard of the time when beta-amyloid was added. As a result, an effect of restraining neuronal cell death, even though the effect was slight, was obtained.

Ginsenosides Rb1 and Rg1, commercially available from Wako Co, were also investigated for their activity against



WO 00/04912

PCT/KR99/00381

the neuronal cell death ascribed to the accumulation of beta-amyloid. For all cases of the pretreatment, the cotreatment and the posttreatment, a potent inhibitory activity against cell death were observed.

5 In more detail, by adding various concentrations of beta-amyloid, believed to be a cause of Alzheimer disease, to media in which neuronal cells were being cultured, there was established the concentration of beta-amyloid at which the neuronal cells started to die. The neuronal cells were  
10 pretreated, cotreated or posttreated with the ginseng extracts with respect to the addition of beta-amyloid and then, cultured for 18 hours, followed by measuring the inhibitory effect of the ginseng extracts on neuronal cell death attributable to beta-amyloid. With regard to the  
15 measurement, an MTT (3-(4,5-dimethyl-2-thiazoly)-2,5-diphenyl-2H-tetrasolium bromide) assay was taken.

MTT assay

WO 00/04912

PCT/KR99/00381

In a culture medium in which neuronal cells were growing, 15µl of an MTT solution were added, after which they were cultured at 37°C for 3-4 hours. The MTT solution was prepared by dissolving 2-5 mg of the MTT reagent per ml of PBS. After being added with 100µl of a solubilization buffer containing 10 % of sodium dodecyl sulfate (SDS) and 50 % of dimethylformaldehyde with pH 4.7, the culture medium was let to stand at room temperature for 24 hours. Then, the medium was measured for absorbance at 570 nm and 630 nm. Since the absorbance at 630 nm was a reference level, the values resulting from subtraction from the absorbance at 570 nm to that at 630 nm were recorded.

The results of the MTT assay are given in Tables 1 and 2, below.

While the absorbance data obtained from the neuronal cell group which was treated with beta-amyloid only, were regarded zero %, the absorbance data from the neuronal cell group which was treated with the ginseng extract components in the absence of beta-amyloid were set as 100 %. When

WO 00/04912

PCT/KR99/00381

neuronal cells were treated with beta-amyloid and ginseng extract both, how many neuronal cells were survived could be represented as relative percentages.

5

TABLE 1

## Efficacy Test of Rb1

Test Nos.	Contr ol	Treated with $\beta$ - amyloid	Treated with Rb1			Treated with Rb1 and $\beta$ -amyloid		
			10nM	50nM	1 $\mu$ l	10nM	50nM	1 $\mu$ l
1	0.095	0.048	0.084	0.079	0.068	0.048	0.051	0.06
2	0.095	0.045	0.084	0.079	0.074	0.047	0.051	0.062
3	0.088	0.05	0.08	0.083	0.086	0.046	0.049	0.076
4	0.086	0.051	0.084	0.079	0.073	0.053	0.047	0.066
Avg.	0.091	0.0485	0.083	0.08	0.075	0.049	0.05	0.066

In Table 1, the control was treated with neither beta-amyloid nor the ginseng extract Rb1. For the neuronal cell

WO 00/04912

PCT/KR99/00381

group treated with beta-amyloid only, 50 $\mu$ M of beta-amyloid were used.

As shown in Table 1, the addition of beta-amyloid had the neuronal cell group begin to undergo a cell death process. However, when a variety of Rb1 concentrations were added to the neuronal cell group which had already undergone a cell death process, the cells were restored to life again, with an increase in the absorbance. Calculating an average, the increase rate obtained was 1.45% upon addition of Rb1 at an amount of 10nM, 4.76% upon addition of Rb1 at an amount of 50nM, and 66.04% upon addition of Rb1 at an amount of 1 $\mu$ M. Consequently, the most potent efficacy against cell death attributed to beta-amyloid was expressed when Rb1 was used at an amount of 1 $\mu$ M in this experiment.

15

TABLE 2

Efficacy Test of Rg1

WO 00/04912

PCT/KR99/00381

Test Nos.	Contr ol	Treated with $\beta$ - amyloid	Treated with Rgl			Treated with Rgl and $\beta$ -amyloid		
			10nM	50nM	1 $\mu$ l	10nM	50nM	1 $\mu$ l
1	0.095	0.048	0.082	0.081	0.085	0.05	0.051	0.074
2	0.095	0.045	0.083	0.082	0.103	0.056	0.052	0.055
3	0.088	0.05	0.08	0.084	0.083	0.046	0.058	0.053
4	0.086	0.051	0.089	0.084	0.086	0.048	0.052	0.065
Avg.	0.091	0.0485	0.084	0.083	0.09	0.05	0.053	0.062

In Table 2, the control was treated with neither beta-amyloid nor the ginseng extract Rgl. For the neuronal cell group treated with beta-amyloid only, 50nM of beta-amyloid  
5 were used.

As shown in Table 2, the presence of beta-amyloid induced the neuronal cell group to undergo apoptosis. However, when a variety of Rgl concentrations were added to the neuronal cell group which had already undergone a cell  
10 death program, the cells were regenerated with an increase in the absorbance. Calculating an average, the increase

WO 00/04912

PCT/KR99/00381

rate of the absorbance was 4.23% upon addition of Rg1 at an amount of 10 nM, 13.03% upon addition of Rg1 at an amount of 50nM, and 32.5% upon addition of Rg1 at an amount of 1μM. Consequently, the most potent efficacy against cell death  
5 attributed to beta-amyloid was expressed when Rb1 was used at an amount of 1μM in this experiment.

#### EXAMPLE II

In this example, after ginsenosides Rb1 and Rg1 were  
10 injected to live mice, a test was made of space perception ability, one of the most representative criteria of dementia, and a cerebrotomy operation was conducted to investigate the synapse density in the brain.

For a space perception ability test, 60 B6 mice were  
15 used. A solution of a ginseng extract containing ginsenoside Rb1 or Rg1 in physiological saline was intraperitoneally injected into the mice at a dose of 1mg per kg of the body weight of the mice at 24 hour intervals for 4 days. After completion of the four-day-

WO 00/04912

PCT/KR99/00381

administration, the behavior of the mice was observed from the fifth day.

In order to test the mice for space perception ability, the Morris water-maze technique was adopted. Testing was conducted twice a day for 5 days while the water was maintained at 21-24 °C. Upon each test, the testees were positioned at any starting point and allowed to discover a platform concealed in the maze. Where the testees did not reach the platform within a maximum of 60 seconds, they were regarded as to have failed the test. If so, the mice were let to be positioned at the platform for 10 seconds. In the course that the mice sought for the platform, the latency, the swimming speed and the swimming trace were recorded at every trial.

With reference to Fig. 1, there is a graph showing the space perception ability change with the trial number for the control and the test groups administered with ginsenosides Rg1 and Rb1. As apparent in this graph, the group administered with ginsenoside Rb1 or Rg1 is superior

WO 00/04912

PCT/KR99/00381

in space perception ability to the control. From the second day of the space perception ability test, the administration of the ginsenosides showed an effect of enabling the mice to reach the platform within shorter periods of time compared  
5 with those of the control. The difference in the latency between the ginsenoside-administered groups and the control got wider as the learning was repeated.

Next, the brains were enucleated from the mice which were administered with the ginsenosides Rg1 and Rb1 and with  
10 physiological saline, in order to examine the density of the synapses therein. To this end, synaptophysin, a representative of synaptic vesicles, which are densely distributed near the cytoplasmic membrane of the presynaptic axon, was quantified and its changes in quantity were  
15 compared between the administered groups and the control. In relation to this change, if the region in which the density of synapses is increased is coincident with the region which is responsible for learning and memory of the brain, the difference in space perception ability between



WO 00/04912

PCT/KR99/00381

pre- and post-administration of the ginsenosides might be believed to be closely connected with the mechanism of increasing the density of synapses in the brain.

As a standard to detect the density of synapses, synaptophysin, a synapse-unique protein, was measured for the level in the brain of the mice which had experienced the space perception ability test, through a Western blotting technique. The target tissue which was suitable for this goal was the hippocampus because it takes charge of the memory of the brain, while the cortex was used for comparison.

With reference to Fig. 2, there are Western blots of synaptophysin 38kDa in molecular weight, obtained from the control and the groups administered with ginsenosides Rb1 and Rg1. As indicated from the Western blots of Fig. 2, both of the groups administered with the ginsenosides Rb1 and Rg1 showed that the level of synaptophysin was increased specifically in the hippocampus, but not in the cortex. For

WO 00/04912

PCT/KR99/00381

the control, no observation was made of the level increase of synaptophysin in the hippocampus.

Amounts of synaptophysin in the brain were measured with the aid of a densitometer, followed by calculating  
5 average values and their standard deviation from the measurements and then, comparing them between the administered groups and the control.

Referring to Fig. 3, there are histograms showing the average synaptophysin levels, along with the standard  
10 deviations, in the hippocampus and the cortex for the control, the Rb1-administered group and the Rg1-administered group. As seen in Fig. 3a, the level of synaptophysin in the hippocampus was increased about 2.1 times for the Rb1-administered group and about 1.8 times for the Rg1-  
15 administered group greater than for the control. In the case of the cortex, which is seen in Fig. 3b, almost no differences in the level of synaptophysin were found among the control, the Rb1-administered group and the Rg1-administered group.

WO 00/04912

PCT/KR99/00381

Taken together, the data obtained in the above examples indicate that the ginsenosides Rb1 and Rg1 of ginseng extracts act specifically on the hippocampus to activate the formation of synapses as well as the signal transduction between synapses, leading to an improvement in the learning and memory. Based on these experimental data, therefore, the present invention verifies the efficacy of the ginsenosides Rb1 and Rg1 as therapeutic agents for dementia.

Further, the present invention provides a basis on which clinical experiments can be carried out to produce dementia-curing agents.

As described hereinbefore, the therapeutic agent for dementia, according to the present invention, based on ginsenoside Rb1 or Rg1, has advantages of being preventive of neuronal cell death ascribed to beta-amyloid, a fundamental factor causing dementia such as Alzheimer disease, and acting specifically on the hippocampus.

WO 00/04912

PCT/KR99/00381

**CLAIMES**

1. A therapeutic agent for dementia, comprising ginsenoside Rb1 or Rg1 as a medicinally effective component.

5

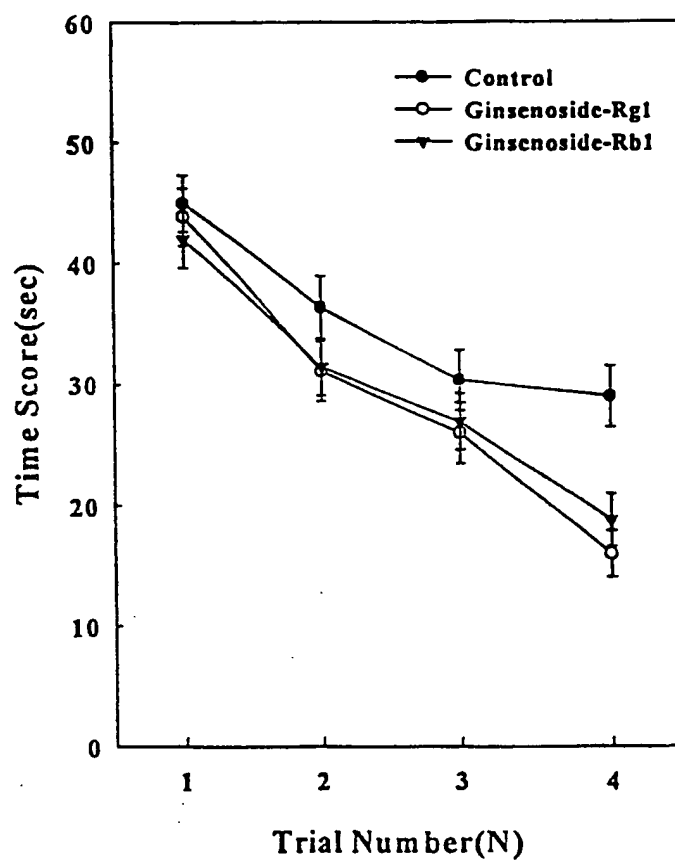
2. A pharmaceutical composition comprising an effective amount of ginsenoside Rb1 or Rg1 together with a pharmaceutically acceptable carrier or diluent.

- 10 3. A method for the treatment of dementia which comprises administering ginsenoside Rb1 or Rg1.

WO 00/04912

PCT/KR99/00381

Fig.1



WO 00/04912

PCT/KR99/00381

Fig.2a

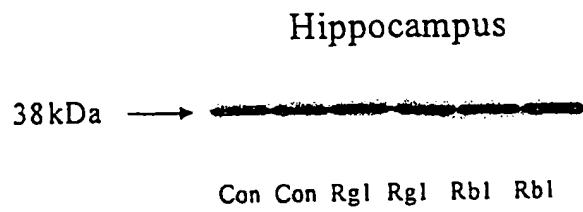


Fig.2b



WO 00/04912

PCT/KR99/00381

Fig.3a

Hippocampus

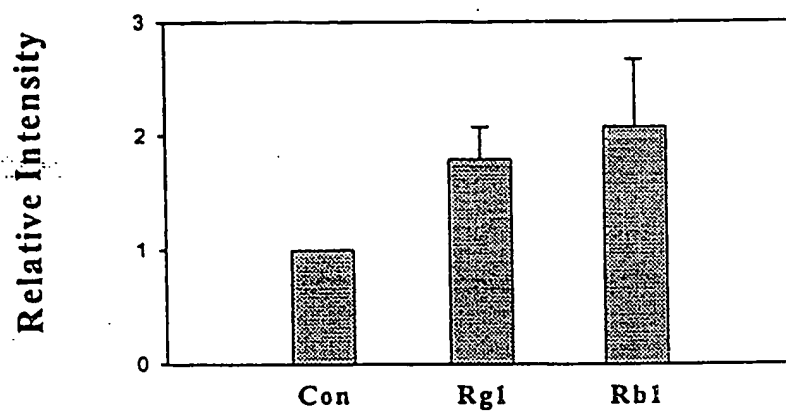
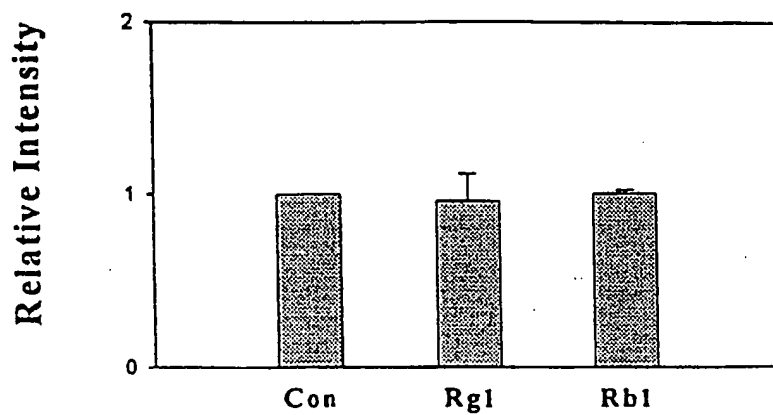


Fig.3b

Cortex



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/KR 99/0381

## A. CLASSIFICATION OF SUBJECT MATTER

IPC<sup>7</sup>: A 61 K 35/78

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC<sup>7</sup>: A 61 K 35/78

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90/08315 A1 (PANG et al.) 26 July 1990 (26.07.90) abstract, claims 4-15.  -----	1-3

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR 99/00381

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 3 concerns a method of treatment of the human or animal body by therapy (see Rule 39.1 (iv) PCT) the search was carried out and based on the alleged effect.

2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

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Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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